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Fragile X Syndrome

The genetic disorder Fragile X syndrome, which results from mutations in a gene on the X chromosome, is the most commonly inherited form of developmental and intellectual disability.

NICHD supports and conducts research on the diagnosis, treatment, management, prevention, and inheritance of Fragile X and its associated conditions, Fragile X-Associated Primary Ovarian Insufficiency (FXPOI) (/health/topics/fxpoi) and Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS) (/health/topics/fxtas). All three conditions result from changes in the same gene on the X chromosome.

About Fragile X Syndrome

Fragile X syndrome is a genetic disorder that affects a person's development, especially that person's behavior and ability to learn. In addition, Fragile X can affect:

- Communication skills
- Physical appearance
- Sensitivity to noise, light, or other sensory information

Fragile X syndrome is the most common form of inherited intellectual and developmental disability (IDD) (/health/topics/idds).

People with Fragile X syndrome may not have noticeable symptoms, or they can have more serious symptoms that range from learning disabilities to cognitive and behavior problems.

How is a change in the FMR1 gene related to Fragile X & associated disorders?

Fragile X syndrome and its associated conditions are caused by changes (mutations) in the *FMR1* gene found on the X chromosome. This mutation affects how the body makes a protein called FMRP. The mutation causes the body to make only a little bit or none of the protein, which can cause the symptoms of Fragile X.

In a gene, the information for making a protein has two parts: the introduction, and the instructions for making the protein itself. Researchers call the introduction the **promoter** because of how it helps to start the process of building the protein.

The promoter part of the *FMR1* gene includes many **repeats**—repeated instances of a specific DNA sequence called the CGG sequence. The *FMR1* gene usually has between 6 and 40 repeats in the promoter; the average is 30 repeats.

People with between 55 and 200 repeats have a **premutation** of the gene. The premutation may cause the gene to not work properly, but it does not cause intellectual and developmental disability (IDD). The premutation is linked to the disorders FXPOI (/health/topics/fxpoi) and FXTAS (/health/topics/fxtas). However, not all people with the premutation show symptoms of FXPOI or FXTAS.

People with 200 or more repeats in the promoter part of the gene have a **full mutation**, meaning the gene might not work at all. People with a full mutation often have Fragile X syndrome.

The number of repeats, also called the "size of the mutation," affects the type of symptoms and how serious the symptoms of Fragile X syndrome will be.

Inheriting Fragile X Syndrome

Fragile X syndrome is inherited, which means it is passed down from parents to children. Anyone with the *FMR1* gene mutation can pass it to their children. However, a person who inherits the gene mutation may not develop Fragile X syndrome. Males will pass it down to all of their daughters and not their sons. Females have a 50/50 chance to pass it along to both their sons and daughters. In some cases, an *FMR1* premutation can change to a full mutation when it is passed from parent to child. Read more about how *FMR1* changes as it is passed from parent to child (/health/topics/fragilex/more_information/faqs#passed).

What causes Fragile X syndrome?

Fragile X results from a change or mutation in the ***Fragile X Messenger Ribonucleoprotein 1*** **(*FMR1*)** gene, which is found on the X chromosome. The gene normally makes a protein, called FMRP, that is important for creating and maintaining connections between cells in the brain and nervous system. The mutation causes the body to make only a little bit or none of the protein, which often causes the symptoms of Fragile X.

Not everyone with the mutated *FMR1* gene has symptoms of Fragile X syndrome, because the body may still be able to make FMRP. A few things affect how much FMRP the body can make:

- **The size of the mutation.** Some people have a smaller mutation (a lower number of repeats) in their *FMR1* gene, while others have big mutations (a large number of repeats) in the gene. If the mutation is small, the body may be able to make some of the protein. Having the protein available makes the symptoms milder.
- **The number of cells that have the mutation.** Because not every cell in the body is exactly the same, some cells might have the *FMR1* mutation while others do not. This situation is called mosaicism. If the mutation is in most of the body's cells, the person will probably have symptoms of Fragile X syndrome. If the mutation is in only some of the cells, the person might not have any symptoms at all or only mild symptoms.
- **Being female.** Females have two X chromosomes (XX), while males have only one. In females, if the *FMR1* gene on one X chromosome has the mutation, the *FMR1* gene on the other X chromosome might not have the mutation. Even if one of the female's genes has a very large mutation, the body can usually make at least some FMRP, leading to milder symptoms.

What are the symptoms of Fragile X syndrome?

People with Fragile X do not all have the same signs and symptoms, but they do have some things in common. Symptoms are often milder in females than in males.

- Intelligence and learning. Many people with Fragile X have problems with intellectual functioning.
  - These problems can range from the mild, such as learning disorders or problems with mathematics, to the severe, such as an intellectual or developmental disability.
  - The syndrome may affect the ability to think, reason, and learn.
  - Because many people with Fragile X also have attention disorders, hyperactivity, anxiety, and language-processing problems, a person with Fragile X may have more capabilities than his or her IQ (intelligence quotient) score suggests.
- Physical. Most infants and younger children with Fragile X don't have any specific physical features of this syndrome. When these children start to go through puberty, however, many will begin to develop certain features that are typical of those with Fragile X.
  - These features include a narrow face, large head, large ears, flexible joints, flat feet, and a prominent forehead.
  - These physical signs become more obvious with age.
- Behavioral, social, and emotional. Most children with Fragile X have some behavioral challenges.
  - They may be afraid or anxious in new situations.
  - They may have trouble making eye contact with other people.
  - Boys, especially, may have trouble paying attention or be aggressive.
  - Girls may be shy around new people. They may also have attention disorders and problems with hyperactivity.
- Speech and language. Most boys with Fragile X have some problems with speech and language.
  - They may have trouble speaking clearly, may stutter, or may leave out parts of words. They may also have problems understanding other people's social cues, such as tone of voice or specific types of body language.
  - Girls usually do not have severe problems with speech or language.
  - Some children with Fragile X begin talking later than typically developing children. Most will talk eventually, but a few might stay nonverbal throughout their lives.
- Sensory. Many children with Fragile X are bothered by certain sensations, such as bright light, loud noises, or the way certain clothing feels on their bodies.
  - These sensory issues might cause them to act out or display behavior problems.

How do healthcare providers diagnose Fragile X syndrome?

Healthcare providers often use a blood sample to diagnose Fragile X. The healthcare provider will take a sample of blood and will send it to a laboratory, which will determine what form of the *FMR1* gene is present.[1]

Prenatal Testing (During Pregnancy)

Pregnant women who have an *FMR1* premutation or full mutation may pass that mutated gene on to their children. A prenatal test allows healthcare providers to detect the mutated gene in the developing fetus. This important information helps families and providers to prepare for Fragile X syndrome and to intervene as early as possible.

Possible types of prenatal tests include:

- Amniocentesis. A healthcare provider takes a sample of amniotic fluid, which is then tested for the *FMR1* mutation.
- Chorionic villus sampling. A healthcare provider takes a sample of cells from the placenta, which is then tested for the *FMR1* mutation.[1]

Because prenatal testing involves some risk to the mother and fetus, if you or a family member is considering prenatal testing for Fragile X, discuss all the risks and benefits with your healthcare provider.

Prenatal testing is not very common, and many parents do not know they carry the mutation. Therefore, parents usually start to notice symptoms in their children when they are infants or toddlers. The average age at diagnosis is 36 months for boys and 42 months for girls.[2]

Diagnosis of Children

Many parents first notice symptoms of delayed development in their infants or toddlers. These symptoms may include delays in speech and language skills, social and emotional difficulties, and being sensitive to certain sensations. Children may also be delayed in or have problems with motor skills such as learning to walk.

A healthcare provider can perform developmental screening to determine the nature of delays in a child. If a healthcare provider suspects the child has Fragile X syndrome, he/she can refer parents to a clinical geneticist, who can perform a

genetic test for Fragile X syndrome.[2]

Citations

1. National Fragile X Foundation. (2012). *Fragile X Syndrome Testing & Diagnosis*. Retrieved June 7, 2012, from https://fragilex.org/understanding-fragile-x/fragile-x-101/testing-diagnosis/
2. Bailey, D. B., Raspa, M., Bishop, E., & Holiday, D. (2009). No change in the age of diagnosis for fragile x syndrome: findings from a national parent survey. *Pediatrics, 124*, 527–533.

What are the treatments for Fragile X syndrome?

There is no single treatment for Fragile X syndrome, but there are treatments that help minimize the symptoms of the condition. Individuals with Fragile X who receive appropriate education, therapy services, and medications have the best chance of using all of their individual capabilities and skills. Even those with an intellectual or developmental disability can learn to master many self-help skills.

Early intervention is important. Because a young child's brain is still forming, early intervention gives children the best start possible and the greatest chance of developing a full range of skills. The sooner a child with Fragile X syndrome gets treatment, the more opportunity there is for learning.

Educational Treatments

Most children with Fragile X can benefit from special education services that are tailored to their particular strengths and weaknesses. Educational treatments should take the child's specific symptoms of Fragile X (/health/topics/fragilex/conditioninfo/commonsymptoms) into account to promote the best learning environment.

Eligibility for Special Education

Most children with Fragile X are eligible for free, appropriate public education under federal law. Although a medical diagnosis does not guarantee access to special education services, most children with Fragile X will have certain cognitive or learning deficits that makes them eligible for services. Parents can contact a local school principal or special education coordinator to learn how to have a child examined to see if he or she qualifies for services under the Individuals with Disabilities Education Act (https://sites.ed.gov/idea/).

Suggestions for Working with Individuals with Fragile X

Everyone with Fragile X is unique. However, those with this disorder often share some particular behaviors and intellectual characteristics. For example, children with Fragile X can easily become overwhelmed by crowds, noise, and touch. Other common characteristics include weak abstract thinking skills and poor quantitative (measuring and counting) skills. However, these children often have unique strengths as well, including visual memory. By taking these unique strengths and weaknesses into account, teachers can promote the best learning for these children.[1]

Suggestions:

- Know the learning style of the individual.
- Develop a consistent daily schedule or routine.
- Use visual signs (pictures, sign language, logos, words) and concrete examples or materials to present ideas, concepts, steps, etc.
- Prepare the individual for any changes in routine by explaining these changes ahead of time, possibly by using visual signs.
- Include functional goals with academic goals; for instance, teach the individual the names of different pieces of clothing as well as how to dress himself/herself.
- Provide opportunities for the child to be active and move around.
- Use computers and interactive educational software.

- Provide a quiet place where the child can first retreat and then regroup.

Teachers can use the National Fragile X Foundation's Lesson Planning Guide for Fragile X (https://fragilex.org/education/lesson-planning-guide/) (/external-disclaimer) to learn more about the best strategies for teaching children with Fragile X.

What Type of Classroom

In general, there are three options for the classroom placement of a child with Fragile X, based on that child's specific abilities and needs:

- Full inclusion in a regular classroom
- Inclusion with "pull-out" services
- Full-time special education classroom

Placement decisions should be based on each child's needs and abilities.

The Individualized Educational Plan (IEP)

If a child with Fragile X syndrome qualifies for special services, a team of people will work together to design an IEP for the child. The team may include parents or caregivers, teachers, a school psychologist, and other specialists in child development or education. The IEP includes specific learning goals for that child, based on his or her needs and capabilities. The team also decides how best to carry out the IEP. It reaches a consensus on classroom placement for the child, determines any devices or special assistance the child needs, and identifies the specialists who will work with the child.

The special services team should evaluate the child on a regular basis. The team can chart progress and decide whether changes in treatment are needed (for instance, changes to the IEP, in classroom placement, or in the services provided).

Citations

1. The National Fragile X Education Project. (2004). *Lesson planning guide for students with fragile X syndrome: A practical approach for the classroom*. San Francisco, CA: The National Fragile X Foundation. Retrieved November 7, 2013, from http://www.fragilex.org/wp-content/uploads/2012/01/Lesson-Planning-Guide-for-Students-with-FXS.pdf (PDF 787 KB)

Therapy Treatments

A variety of professionals can help individuals with Fragile X syndrome and their families manage the symptoms of the disorder. Those with Fragile X might benefit from services provided by several different specialists:

- Speech-language therapists can help people with Fragile X syndrome improve their pronunciation of words and sentences, slow down their speech, and use language more effectively.
- Occupational therapists help find ways to adjust tasks and conditions to match a person's needs and abilities.
- Physical therapists design activities and exercises that help build motor control and improve posture and balance.
- Behavioral therapists try to understand why someone with Fragile X acts out, and they create ways and strategies for avoiding or preventing these situations from occurring while also teaching better or more positive ways to respond to situations.

Medication Treatments

To this point, the Food and Drug Administration (FDA) has not approved any drugs specifically for the treatment of Fragile X or its symptoms. But in many cases, medications are used to treat certain symptoms of Fragile X syndrome, as shown in the chart below. NICHD does not endorse or support the use of any of these medications in treating the symptoms of Fragile X syndrome, or for other conditions for which the medications are not FDA approved.

Medication is most effective when paired with therapy designed to teach new coping or behavioral skills. Not every medication helps every child.

Please note that some of these medications carry serious risks. Others may make symptoms worse at first, or they may take several weeks to become effective. Doctors may have to try different dosages or combinations of medications to find the most effective plan. Families, caregivers, and doctors need to work together to ensure that a medication is working and that the medication plan is safe.

This chart is meant for reference ONLY and should not take the place of a healthcare provider's advice. Discuss any questions about medication with a healthcare provider.

Symptom	Generic Medication (Brand Name in Parentheses)
Seizures Mood instability	• Carbamazepine (Tegretol) • Valproic acid or Divalproex (Depakote) • Lithium carbonate • Gabapentin (Neurontin) • Lamotrigine (Lamictal) • Topiramate (Topamax), Tiagabine (Gabitril), and Vigabatrin (Sabril) • Phenobarbital and Primidone (Mysoline) • Phenytoin (Dilantin)

Attention deficit (with or without hyperactivity)	• Methylphenidate (Ritalin, Concerta) and Dextroamphetamine (Adderall, Dexedrine) • L-acetylcarnitine • Venlafaxine (Effexor) and Nefazodone (Serzone) • Amantadine (Symmetrel) • Folic acid
Hyperarousal Sensory overstimulation (often occurs with ADD/ADHD)	• Clonidine (Catapres TTS patches) • Guanfacine (Tenex)
Aggression Intermittent explosive disorder Obsessive-compulsive disorder (often occurs with anxiety and/or depression)	• Fluoxetine (Prozac) • Sertraline (Zoloft) and Citalopram (Celexa) • Paroxetine (Paxil) • Fluvoxamine (Luvox) • Risperidone (Risperdal) • Quetiapine (Seroquel) • Olanzapine (Zyprexa)
Sleep disturbances	• Trazodone • Melatonin

ADD: attention deficit disorder; ADHD: attention deficit hyperactivity disorder; TTS: transdermal therapeutic system.

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